IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Sanberg et al.	Examiner: Daniel E. Kolker
Serial No.:	10/009,036	Group Art Unit: 1649
Filed:	September 30, 2002	Confirmation #: 5509
Docket No.:	LAY-014PCTUS	
Title:	Cell Therapy for Chronic Stroke	

DECLARATION BY LAWRENCE R. WECHSLER, M.D.

Mail Stop Amendment.
Commissioner for Patents
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Alexandria, VA 22313-1450

Dear Examiner:

I am providing this declaration in support of U.S. Application Serial No. , to which an Office Action dated November 23, 2007, rejected all claims on the basis of U.S. Section 103.

1. I am a physician and a board-certified neurologist. I obtained my bachelor degree in Biology from Harvard College and my medical degree from the University of Pennsylvania. I completed an internship and residency in internal medicine at UPMC and did my neurology residency at Massachusetts General Hospital, where I also completed a fellowship in cerebrovascular disease. At the University of Pittsburgh, I am Professor of Neurology and Neurological Surgery, Vice-Chairman of Clinical Affairs, and Director of the UPMC Stroke Institute. I have authored or co-authored many papers and chapters on stroke and stroke treatment. While I participated in the anti-stroke study described in the above-mentioned patent application and received the usual compensation, I have no financial interest in the patent application.

2. I have treated stroke patients for 25 years. Prior to the invention date, I participated in a number of unsuccessful stroke clinical studies of new chemical entities (NCE) that had been successful in experimental animals, such as rodents. We are discovering the reasons for that lack of success. "There are numerous differences between rodents and humans that make the unqualified translation of rodent data inadequate. The most relevant differences .. are manifested as differences in pharmacological, biochemical, developmental, behavioral and functional responses.." (Wakeman DR et al. Editorial: Large animal models are critical for rationally advancing regenerative therapies. FUTURE MEDICINE 2006; 1(4):405-13). "Neuroprotective drugs.. have shown great promise in preclinical testing but disappointment in clinical trials. Of >49 neuroprotective agents studies in >114 stroke trials, **NONE** has proven successful clinically." (Gladstone DJ, et al. Comments: Toward Wisdom From Failure: Lessons from Neuroprotective Stroke Trials and New Therapeutic Directions. STROKE 2002; 33:2123-36; emphasis added)

3. Effective treatments of stroke have been a long-felt need. Hundreds of thousands of patients in the US alone experience strokes. Millions more are still suffering the after effects of those strokes. Numerous experiments in animals and humans have been performed. As of the invention date, none of these clinical studies were successful, except for the study of LBS cells in patients with chronic stroke.

4. Many clinicians and researchers with whom I communicate regularly have been highly disappointed in the lack of efficacy in humans after successful experiments in rodents and other species commonly used in preclinical studies. The Stroke Therapy Academic Industry Roundtable (STAIR) was formed to address those concerns. Although I was not a Statement Contributor on the first article (Recommendations for Standards Regarding Preclinical Neuroprotective and Restorative Drug Development. STROKE 1999; 30:2752-2758), I was a Contributor on the follow-up statement of 2006 (Fisher M et al., Advances in Stroke: Recommendations from the STAIR V Meeting on

Acute Stroke Trials, Technology and Outcomes. STROKE 2007; 38:245-248). The other clinicians, researchers and I have met almost annually since 1999.

5. The results of these meetings were the articles mentioned above. We included our efforts to estimate the number of new chemical entities that had been successful in humans and we could think of NONE. Therefore, we can state that as of 1999, preclinical studies in rodents had NO POSITIVE PREDICTABILITY in humans.

6. I am familiar with the abstract by Dr. Sanberg, Weiss' patent, etc. All these pertain only to animal (rodent) tests that have not been predictive of success in people. The Weiss patent features only a hypothetical example of treatment of humans. The inventors of the instant patent were the first to achieve successful stroke treatment in humans.

7. All the prior literature can be characterized as describing unmet needs because they all aspire to human use with only rodent experiments or hypothetical human implants (the Weiss patent). Furthermore, the STAIR article in 1999 emphasized the unmet need of treatments of stroke, and the failure of conventional tests to predict success in humans. The STAIR article ended with recommendations to do more tests and tests in multiple facilities. However, the article mentioned the continuing use of rodent MCAO tests, only because it represented the *status quo* to be used in the absence of animal models actually correlating with the human response. The article at no point stated that it was a predictive test.

8. The Office Action also stated that it was obvious to one of ordinary skill in the art to administer the cells to multiple points in the brain because that would minimize inflammation due to trauma at any one site. On the contrary, we know that the greater number of injured locations (particularly at the same time) raises the chances of inflammation because each of the separate locations now may become inflamed. Therefore, the success of administration of cells to multiple points in the brain was not

predictable. Furthermore, no patients that we examined showed inflammation on serial MRI or PET scan (Kondziolka D. et al., Transplantation of cultured human neuronal cells for patients with stroke. NEUROLOGY 2000; 55:565-69).

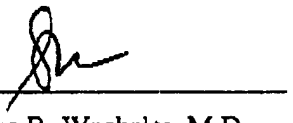
9. The Office Action also stated that it would be obvious to one of ordinary skill in the art to scale up the dose of cells in rodents by quantities per kilogram to the weight of an average human. Dosing is an art in itself; in many cases it is not sufficient to scale up on the basis of quantity per kilogram. "In PD [Parkinson's Disease] for example, it has been estimated that for each volume of tissue innervated by a rat dopaminergic (DA) neuron, a monkey neuron must innervate 20 times that volume, while humans would need a staggering volume of 200 units to mimic similar reinnervation of nigrastriatal projections." (Wakeman DR et al. Editorial: Large animal models are critical for rationally advancing regenerative therapies. FUTURE MEDICINE 2006; 1(4):405-13). For example, neuroprotective drug dose ranges and toxicities in animals may not overlap with those tolerated in humans (STAIR, citing Muir and Lees, Clinical experience with excitatory amino acid antagonist drugs. STROKE 1994; 25:1755-59). The Office Action cited multiplication of Dr. Sanberg's optimal dose would result in 10 million cells. This is almost twice as much as appeared beneficial in our study. Therefore, the dose was not obvious to one of ordinary skill in the art.

10. In conclusion, I believe that LBS neurons for treating chronic stroke in humans are far superior to what is disclosed in the prior art for the following reasons we cited in Nelson P.T. et al., AMER J PATH 160:1201-06, 2002:

> "They 1) do not pose ethical or legal problems because they are not derived from human embryos; 2) are highly uniform unlike cells cultured from living animals; 3) do not harbor known human pathogens or potentially infectious agents present in xenografts; 4) are available in unlimited quantities produced in accordance with good manufacturing practices for human use; 5) have been extensively characterized in vitro and are amenable to genetic engineering; and 6) have been transplanted and characterized previously in normal rodents as well as in animal models of stroke, Huntington's disease, Parkinson's disease and trauma, with encouraging results."

I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Respectfully submitted,



5/12/08

Lawrence R. Wechsler, M.D. Date